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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,142	03/01/2002	Lakshmi Rambhatle	093/005P	3039

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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,142	RAMBHATLE ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13 and 21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/1/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/15/05 has been entered.

Applicants' Amendment and Remarks, filed 11/15/05 have been entered. Claim 1, 2, 14-20 are cancelled; claim 13 has been amended; claims 21-28 are newly added; claims 13, 21-28 are pending and under current examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13, 21-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-15, 19-24, 28-32, 34-38 of copending Application No. 10/001,267. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 3/28/05.

Applicants acknowledge the double patenting rejection, state that it is moot, and that it is only provisional at this point and request abeyance of the rejection until issuance of the '267 application. See Response, p. 3.

These arguments are considered, but not persuasive. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of differentiating pPS cells into differentiated cells that have the morphological features of hepatocytes. The instant claims are directed to methods for producing hepatocytes lineage cells by culturing the pPS cells in a growth environment that comprises one or more hepatocytes maturation factors that are either an organic solvent selected from DMSO, DMA, hexamethylene biascetamide, and other polymethylene bisacetamides; or b) a cytokine or hormone selected from glucocorticoids, EGF, insulin, TGF-α, TGF-β, FGF, HGF, IL-1, IL-6, IGF-II and HBGF-1. The '267 claims are directed to producing differentiated cells from primate pluripotent stem cells by culturing the pPS cells in butyrate, and in specific embodiments, the differentiation is initiated by culturing the cells in DMSO, DMA, hexamethylene biascetamide, and other polymethylene bisacetamides (claim 20) and further, culturing the cells in a medium containing a cytokine or hormone (claim 21).

The instant claims differ from those of the '267 application in that they do not specifically recite using butyrate in order to differentiate the pPS cells. However, using the '267 specification as a dictionary to define the growth environment to differentiate the pPS cells, Table 12 (page 45) clearly shows using the variously recited solvents (for example, DMSO), with butyrate, and various of the recited cytokines or hormones (for example, TGF-α) in order to differentiate to hepatocytes, which are hepatic lineage cells. See Protocol number 1. Furthermore, the '267 claims provide these embodiments (see claims 20 and 21, for example), to produce hepatocytes. Therefore, it would have been obvious to modify the method of claim

13, wherein the medium contains butyrate, to include any of the organic solvents or cytokines/hormones, as instantly claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 13, 21-23, 25, 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6-8, 19-22 of copending Application No. 10/810,311. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of differentiating pPS cells into differentiated cells that have the morphological features of hepatocytes. The instant claims are directed to methods for producing hepatocytes lineage cells by culturing the pPS cells in a growth environment that comprises one or more hepatocytes maturation factors that are either an organic solvent selected from DMSO, DMA, hexamethylene biascetamide, and other polymethylene bisacetamides; or b) a cytokine or hormone selected from glucocorticoids, EGF, insulin, TGF-α, TGF-β, FGF, HGF, IL-1, IL-6, IGF-II and HBGF-1. The '311 claims are directed to processes of differentiating pPS cells into hepatocyte lineage cells by culturing undifferentiated pPS cells to differentiate into fetal endoderm cells, culturing these cells to differentiate into hepatocyte progenitor cells and then to culture the resultant progenitor cells to produce mature hepatocytes. Specific embodiments contemplate utilizing the same culture conditions as the instantly claimed invention (for example, DMSO, in claim 5, and EGF in claim 6).

The instant claims differ from those of the '311 application in that they do not specifically recite using butyrate in order to differentiate the pPS cells. However, using the '311 specification as a dictionary to define the growth environment to differentiate the pPS cells, Table 7 (page 31) clearly shows using the variously recited solvents (for example, DMSO), with butyrate, and various of the recited

cytokines or hormones (for example, TGF-α) in order to differentiate to hepatocytes, which are hepatic lineage cells. See Protocol numbers 7-9. Therefore, it would have been obvious to modify the method of claim 13, wherein the medium contains butyrate, to include any of the organic solvents or cytokines/hormones, as instantly claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101/112

The prior rejection of claims 1 and 3-20 under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph is withdrawn in view of Applicants' cancellation or amendment to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 21-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for obtaining hepatocytes lineage cells, by culturing primate pluripotent stem cells in a grown environment that comprises butyrate or an analog of butyrate, a) an organic solvent selected from DMSO, DMA, hexamethylene biascetamide, and other polymethylene bisacetamides; or b) a cytokine or hormone selected from glucocorticoids, EGF, insulin, TGF-α, TGF-β, FGF, HGF, IL-1, IL-6, IGF-II and HBGF-1.

The specification does not reasonably provide enablement for the breadth of the claims, which are directed to the production of hepatocyte lineage cells in the absence of butyrate or an analog of butyrate. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claimed invention is directed to methods for obtaining hepatocytes lineage cells by culturing pPS (primate pluripotent stem) cells in a growth environment that comprises one or more hepatocytes maturation factors, that are either: a) an organic solvent selected from DMSO, DMA, hexamethylene biascetamide, and other polymethylene bisacetamides; or b) a cytokine or hormone selected from glucocorticoids, EGF, insulin, TGF-α, TGF-β, FGF, HGF, IL-1, IL-6, IGF-II and HBGF-1

Breadth of the claims. The claims broadly encompass using a particular organic solvent, or a cytokine or hormone, delineated above, in order to differentiate primate pluripotent stem cells into hepatocytes lineage cells.

Guidance of the Specification/The Existence of Working Examples. The specification teaches a system for the efficient production of hepatocytes lineage cells from primate pluripotent stem (pPS) cells. (p. 4, lines 1-6). The specification teaches that these cells are cultured in a growth environment that comprises a hepatocytes differentiation factor (such as n-butryate) and can include hepatocytes maturation factors, such as solvents such as DMSO, or growth factors such as FGF, EGF, etc. (page 4, lines 18-27). The working examples teach the differentiation of human ES cells by comparing different culture conditions, including fetal bovine serum (FBS) with n-butryate, FBS with DMSO, dexamethazone, insulin and glucagon, and FBS alone (see Example 1), the specification teaches that using n-

butyrate produced cells which had morphology similar to hepatocytes, whereas using DMSO with growth factors produced a heterogeneous population of cells (page 38, lines 5-12 and Table 4). Table 7 shows the RT-PCR analysis of various expression markers from the cells produced in the conditions outlined in Example 1. The specification teaches using other potential hepatocyte differentiation agents and compares the induction of the hepatocyte phenotype (Table 7), and states that Example 6 teaches the effects of using sodium n-butyrate in combination with DMSO (see Table 9), stating that in all the conditions, the cells looked morphologically alike, but there were fewer colonies of cells in the set where butyrate and DMSO were used together, than with only butyrate alone (see p. 45, lines 2-5).

State of the Art/Predictability of the Art. Verfaillie *et al.* [**Hematology** (Am Soc Hematol Educ Program). 2002;:369-91] who review the state of the art of stem cells at the time of filing, teach, that, with regard to the directed differentiation of ES cells, "Many proposed applications of human ES cells are predicated on the assumption that it will be possible to obtain pure populations of differentiated cells from the ES cultures. It might be envisioned that in order to achieve this one would treat ES cells with inducing agents that would convert them with high efficiency to a cell type of interest. In practice, that has not proven possible with the mouse system." See p. 278, 2nd column, Differentiation in vitro. Verfaillie teach that the ES cells can be treated with particular agents/factors that can drive differentiation along a specific lineage (see p. 379, 1st column, 1st full ¶. However, it is clear that directed differentiation of ES cells to generate a particular cell type of interest is unpredictable. Thus, specific guidance must be provided to enable the claimed invention.

The Amount of Experimentation Necessary. The claims are not enabled for their breadth, because the state of the art of directed differentiation of ES cells to a particular cell type, is not found to be predictable, and the working examples in the

specification fail to support that culturing pPS cells with either an organic solvent, or a cytokine, alone (as instantly claimed) would result in hepatocyte lineage cells. Example 1, which uses DMSO and insulin, teaches that the cells are "remarkably heterogenous" and does not provide any teachings for hepatocyte lineage cells. Furthermore, the example clearly shows that sodium butyrate is essential to produce hepatocytes (see p. 38, lines 5-10). The other working examples in the specification provide further evidence that sodium butyrate is a hepatocyte differentiation factor, whereas the organic solvents and cytokines that are instantly claimed, are considered hepatocyte maturation factors (see example 3). The enabled scope of the claims is limited to using butyrate or an analog thereof, because the working examples show that analogs of butyrate (including butyric acid, propionic acid, isovaleric acid, and isobutyric acid) were capable of inducing pPS cells to differentiate into hepatocytes (see p. 42, lines 8-11 and Table 7). Thus, one of skill in the art would be able to, without undue experimentation, utilize butyrate, or an analog of butyrate, in order to produce hepatocyte lineage cells. The specification clearly shows that butyrate can be used in combination with DMSO (Example 6), but DMSO or any of the organic solvents or cytokines cited in the instant claims; however, by themselves, fail to produce the hepatocyte phenotype, which requires butyrate to induce differentiation. Example 9, Table 12, recites direct differentiation protocols, and specifically show that, under conditions which do not contain DMSO, but various cytokines and hormones and in the presence of butyrate produce hepatocytes (see Figure 5, p. 48-49 bridging ¶).

Thus, given the state of the art, with regard to the unpredictability of directing differentiation of ES cells to a particular cell type, the working examples, which teach that butyrate (or an analog of butyrate) is required to induce the hepatocyte phenotype, the breadth of the claims, which fail to recite butyrate in the growth environment, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

The prior rejection of claim 2 under 35 U.S.C. 102(b) as being anticipated by Chen et al., Hoshi et al. or Kono et al. is withdrawn in view of Applicants' cancellation of the claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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